Scholars Academic Journal of Pharmacy (SAJP) **ISSN 2320-4206 (Online)**
Sch. Acad. J. Pharm., 2014; 3(2): 128-132 **ISSN 2347-9531 (Print)**

(An International Publisher for Academic and Scientific Resources)
www.saspublisher.com

Research Article

Synthesis, Characterization and Evaluation of Anticonvulsant activity of some Novel 4-Thiazolidinone Derivatives

Asish Bhaumik[1*], M. Ashok Chandra[1], Shubhankar Saha[2], Juturu Mastanaiah[2], Telu Visalakshi[2]
[1]Teja College of Pharmacy, Department of Pharmaceutical Chemistry & Pharmaceutical Analysis, Kodad, Nalgonda (Dist.)-508206, Andhra Pradesh, India
[2]GATE School of Pharmacy, Department of Pharmacology & Pharmaceutical Analysis, Kodad, Nalgonda (Dist.)-508206, Andhra Pradesh, India

***Corresponding author**
Asish Bhaumik
Email: bhaumik.asish@gmail.com

Abstract: The objective of the present work is the synthesis of N-[2-(4-substituted phenyl)-4-oxo-1,3-thiazolidine-3-yl]-2-(naphthalene-2-yloxy)acetamide and evaluation of anticonvulsant activity. Based on this a new series of compound have been planned to synthesize by reacting β-napthol,ethyl chloroacetate, hydrazinemonohydrate, ethyl alcohol and various aromatic aldehydes. The anticonvulsant activity of the test drugs were evaluated by using MES induced convulsions in mice. The percentage protection was estimated by observing the number of animals showing abolition of Hind Limb Tonic Extension (HLTE) or extension not greater than 90°. The synthetic derivatives (A9,A8,A2,A1&A10) 200 mg/kg have shown 95.85%, 90.04% ,84.23%, 79.75% & 73.44% protection against MES induced seizure respectively.
Keywords: Anticonvulsant activity, HLTE, MES, Seizure, 4-Thiazolidinone Derivatives

INTRODUCTION

4-thiazolidinones are the derivatives of thiazolidine with a carbonyl group at the 4 position. Several methods for the synthesis are available.The synthesis of 2-amino 4-thiazolidinones-4-C has been reported by using thiourea and sodium salt of labeled monochloroacetic acid [1]. Another method of synthesis of 4-thiazolidinones is by using of thiocyanate, alkylisothiocyanate with hydrazide/acetamide followed by the treatment with ethylchloro or ethylbromo acetate and sodium acetate [2].

The literature survey revealed that 4-thiazolidinone and their derivatives were possessed a wide range of pharmacological activities such as anti-inflammatory, analgesic, anticonvulsant, antimicrobial, local and spinal anesthetics, CNS stimulants, hypnotics, anti HIV, anti diabetic, anticancer, FSH receptor antagonist and CFTR inhibitor etc [3, 4].

The objective of the present work is the synthesis of N-[2-(4-substituted phenyl)-4-oxo-1,3-thiazolidine-3-yl]-2-(naphthalene-2-yloxy)acetamide and evaluation of anticonvulsant activity. Based on this a new series of compound have been planned to synthesize by reacting β-napthol,ethylchloroacetate, hydrazinemonohydrate, ethylalcohol and various aromatic aldehydes.

MATERIALS AND METHODS

The all chemicals used for the synthesis were of laboratory grade and analytical grade. The melting points of newly synthesized thiazolidinone derivatives were determined by open capillary method. The IR spectra of synthesized compounds were recorded by ABB Bomen FT-IR spectrometer MB 104 IR spectra recorder with KBr pellets. The H^1-NMR spectra of synthesized compounds were recorded by BRUKER NMR spectrometer in DMSO. The Mass spectra of synthesized compounds were recorded by JEOL GC mate. The purification of newly synthesiszed compounds were done by TLC method. TLC plates are pre-coated silica gel (HF254-200 mesh) aluminium plate using ethyl acetate & n-hexane as an solvent system and spots were visualized under U.V. chamber. The IR, H^1 – NMR and Mass spectra were assigned to elucidate the structure of synthesized compounds (A1 – A10).

Steps involved in the Synthesis of Compounds [5-7]

First step: Preparation of ethyl-2-naphthalene -6-yloxy acetate

2-napthol (1.44 gm, 10 mmol), anhydrous potassium carbonate (1gm) and ethylchloro acetate (1.67gm, 10mmol) in 50ml of anhydrous acetone were refluxed on oil bath for 6 hours. The reaction mixture was

filtered and the excess solvent was removed by distillation under pressure.

Second step: Preparation of 2-(naphthalene-6-yloxy) acetohydrazide

The residue and 1gm hydrazine monohydrate (20 mmol) were dissolved in 50 ml of absolute ethanol and refluxed on a steam bath for 1 hour. The solute must was filtered and dried and recrystalized from ethanol.

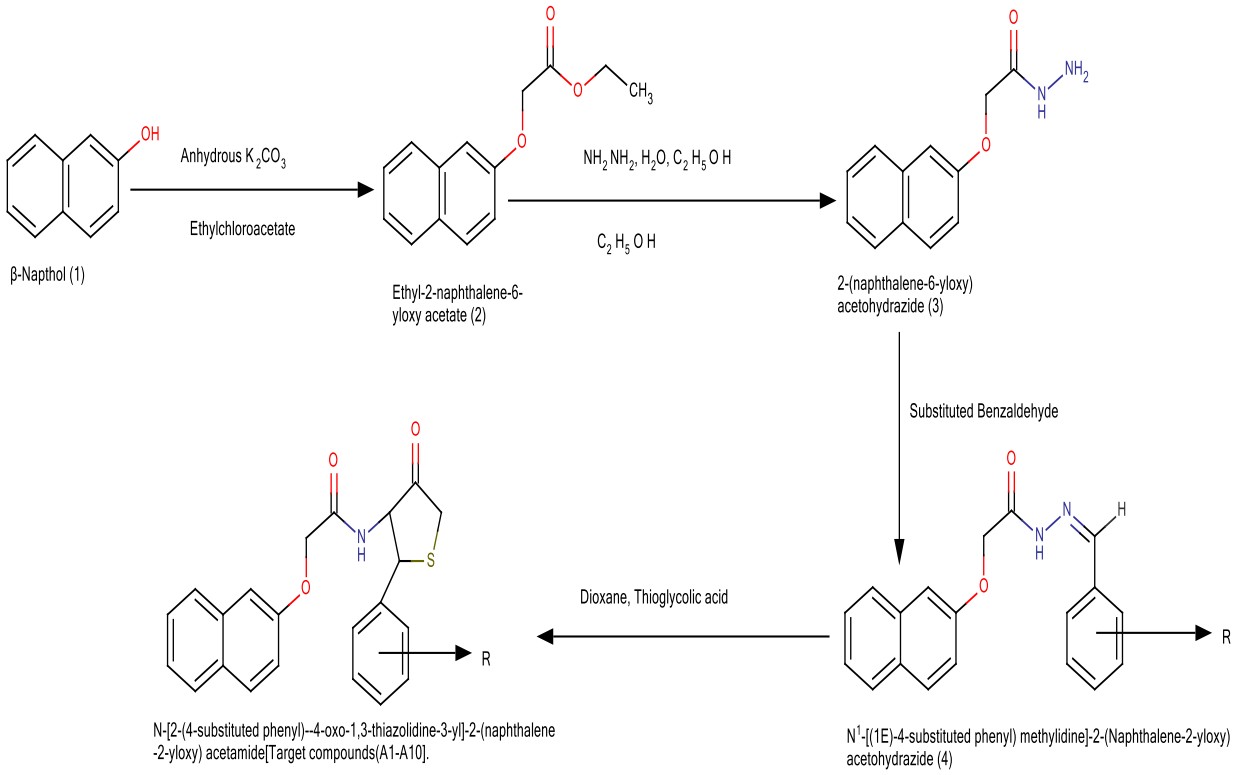
Third step: Preparation of substituted benzaldehyde derivatives

0.01mol of substituted benzaldehyde and 0.01mol of substance and 2-3 drops of glacial acetic acid and 20ml of ethanol were taken in round bottom flask and reflux for 6 hours on water bath. After cooling add ice cold water to the mixture to give solid white mass. Filtered and dried. Recrystalized from chloroform-methanol mixture.

Fourth step: General method of synthesis of thiazolidinone derivatives

A mixture of Schiff base (0.001mmol) and Thioglycolic acid (0.001mol) dissolved in 1,4-dioxane (20ml), anhydrous zinc chloride (0.5mg) was added and refluxed for 8 hours. The reaction was then cooled to 30°C and the resultant solid was washed with sodium bicarbonate solution. The final compound recrystalized from absolute ethanol.

Synthetic Scheme



Compound A1: N-[2-(4-hydroxyphenyl]-4-oxo-1,3-thiazolidin-3-yl-2-(naphthalene-2-yloxylacetamide. M.F- $C_{21}H_{18}N_2O_4S$, M.W 394.44 ,M.P-180^{O}c, R_f-0.55, Yield-62.1%, IR (KBr) ν (cm^{-1}): 1624.11cm^{-1}(Ar-C=C),3177.12cm^{-1}(aliph-N-H),1026.57cm^{-1}(N-N),747.42cm^{-1}(C-S),3610.57cm^{-1}(O-H phe),1689.24cm^{-1}(C=O),1269.54cm^{-1}(C-N),1728.62cm^{-1}(C=O-thiazolidine), ^{1}H-NMR δ (ppm): 8.0(1H,-NH-),6.8-7.9(11H,Ar-H),5.92(1H,-N-CH-S-),5.21(1H,Ar-OH),5.0(2H,-O-CH_2-CO-),3.8(2H,-S-CH_2), Mass (m/e value): 394.5(30%)(M^+), 395.4(25%)(M+1), 377.1(50%), 301.0(70%), 274.0(38%), 228.1(58%), 200.7(67%), 185.1(24%), 157.1(48%), 127.1(73%), 102.0(44%),100.4(100%)B

Compound A2: N-[2(4-chlorophenyl-4-oxo-1,3-thiazolidin-3-yl]-2-(naphthalene-2-yloxy)acetamide. M.F: $C_{21}H_{17}ClN_2O_3S$, MW-412.89, M.P-172^{0}c, R_f-0.46, Yield-65.2%, IR (KBr) ν (cm^{-1}): 1611.20cm^{-1} (Ar-C=C) ,3186.99cm^{-1} (Aliph-N-H), 1086.99cm^{-1} (N-N) ,695.56cm^{-1} (C-S) ,1668.87cm^{-1}(C=O), 1267.68cm^{-1} (C-N) ,750.35cm^{-1} (Ar-C-Cl) ,1716.32cm^{-1} (C=O-thiazolidine), ^{1}H-NMR δ (ppm): 8.3 (1H,-NH-) ,6.8-7.9 (11H,Ar-H) ,5.80 (1H,-N-CH-S-) ,5.0 (2H,-O-CH_2-CO-), 3.3(2H,-S-CH_2), Mass (m/e value): 412.9(24%)(M^+), 413.8(20%)(M+1), 377.1(50%), 301.0(70%), 274.0(38%), 228.1(58%), 200.7(67%), 185.1(24%), 157.1(48%), 127.1(73%), 102.0(44%),100.4(100%)B.

Compound A3: N[2-(4-fluorophenyl)-4-oxo-1,3-thiazolidin-3-yl]-2-(naphthalene)acetamide. M.F- $C_{21}H_{17}FN_2O_3S$, MW- 396.43, M.P-175^{0}c, R_f- 0.48, Yield- 55.7%, IR (KBr) ν (cm^{-1}): 1609.09cm^{-1}(Ar-C=C),3194.42cm^{-1}(Aliph-N-H),1026.76cm^{-1}(N-N)**,**1256.34cm^{-1}(C-N),705.10cm^{-1}(C-S),1662.09cm^{-1}(C=O), 1000.62cm^{-1}(Ar-C-F),1721.94cm^{-1}(C=O-thiazolidin), ^{1}H-NMR δ (ppm): 8.20(1H,-NH-),6.8-7.9(11H,Ar-H),6.0(1H,-N-CH-S-),4.90(2H,-O-CH_2-CO-),3.5(2H,-S-CH_2-), Mass (m/e value): 396.5 (13%)(M^+), 397.4(11%)(M+1), 377.1(50%), 301.0(70%), 274.0(38%), 228.1(58%), 200.7(67%), 185.1(24%), 157.1(48%), 127.1(73%), 102.0(44%),100.4(100%)B.

Compound A4: N-[2-(4-bromophenyl)-4-oxo-1,3-thiazolidin-3-yl]-2-(naphthalene-2-yloxy)acetamide. M.F- $C_{21}H_{17}BrN_2O_3S$, M.W-457.34, M.P- 178^{0}c, R_f-0.51, Yield- 64.96%, IR (KBr) ν (cm^{-1}): 1621.73cm^{-1}(Ar-C=C), 3198.97 cm^{-1}(Aliph-N-H), 1031.38 cm^{-1}(N-N), 758.36 cm^{-1}(C-S), 1681.77 cm^{-1}(C=O), 1530.18 cm^{-1}(Ar-C-Br), 1721.46 cm^{-1}(C=O-thiazolidine), ^{1}H-NMR δ (ppm): 8.0(1H,-NH-), 6.8-7.9(11H,Ar-H), 5.9(1H,-N-CH-S-), 5.2(2H,-O-CH_2-CO-), & 3.3(2H,-S-CH_2-), Mass (m/e value): 457.4(10%)(M^+), 458.3(9%)(M+1), 377.1(50%), 301.0(70%), 274.0(38%), 228.1(58%), 200.7(67%), 185.1(24%), 157.1(48%), 127.1(73%), 102.0(44%),100.4(100%)B.

Compound A5: 2-(naphthalene-2-yloxy)-N-[2-(4-nitrophenyl)-4-oxo-1,3-thiazolidin-3-yl]acetamide. M.F- $C_{21}H_{17}N_3O_5S$, M.W- 423.44, M.P- 160^{0}c, R_f-0.71,Yield- 68.2%, IR (KBr) ν (cm^{-1}): 1605.0cm^{-1}(Ar-C=C), 3181.81 cm^{-1},(Aliph-N-H), 1050.57 cm^{-1}(N-N), 1248.07 cm^{-1}(C-N), 752.45 cm^{-1}(C-S), 1685.27 cm^{-1}(C=O), 1521.57 cm^{-1}(Ar-NO_2), 1721.09 cm^{-1}(C=O-thiazolidine), ^{1}H-NMR δ (ppm): 8.2(1H,-NH-), 6.8-7.9(11H, Ar-H), 5.8(1H,-N-CH-S-), 5.1(2H, -O=CH_2-CO-), & 3.4(2H, -S-CH_2-), Mass (m/e value) **:** 423.5(11%)(M^+), 424.4(9%)(M+1), 377.1(50%), 301.0(70%), 274.0(38%), 228.1(58%), 200.7(67%), 185.1(24%), 157.1(48%), 127.1(73%), 102.0(44%),100.4(100%)B.

Compound A6: 2(naphthalene-2-yloxy)-N-[2-nitrophenyl)-4-oxo-1,3-thiazolidin-3-yl]acetamide. M.F- $C_{21}H_{17}N_3O_5S$, M.W- 423.44, M.P- 165^{0}c, R_f- 0.69, Yield- 68.2%, IR (KBr) ν (cm^{-1}): 1613.0cm-1(Ar-C=C), 3211.27 cm-1(Aliph-N-H), 1061.45 cm-1(N-N), 1248.01 cm-1(C-N), 774.86 cm-1(C-S),1681.31 cm-1(C=O),1516.23 cm-1(NO_2), 1717.68 cm-1(C=O-thiazolidine), ^{1}H-NMR δ (ppm): 8.2(1H, -NH-), 6.8-7.9(11-H, Ar-H), 5.8(1H,-N-CH-S-), 5.2(2H,-O-CH_2-CO-),3.4(2H, -S-CH_2-), Mass (m/e value): 423.5(9%)(M^+), 424.4(8%)(M+1), 377.1(50%), 301.0(70%), 274.0(38%), 228.1(58%), 200.7(67%), 185.1(24%), 157.1(48%), 127.1(73%), 102.0(44%),100.4(100%)B.

Compound A7: N-[2-(3,4-dimethoxyphenyl)-4-oxo-thiazolidin-3-yl]-2-(naphthalene-2-yloxy)acetamide. M.F- $C_{23}H_{22}N_2O_5S$,M.W-438.12, M.P-185^{0}c, R_f-0.66, Yield-58.6%, IR (KBr) ν (cm^{-1}): 1619.0cm-1(Ar-C=C), 3202.17cm-1(Aliph-N-H), 1026.57cm-1(N-N), 1265.59cm-1(C-N), 747.42cm-1(C-S), 1663.99cm-1(C=O), 1126.82cm-1(-C-O-C-), 1723.15cm-1(C=O-thiazolidine), ^{1}H-NMR δ (ppm): 8.2(1H, -NH-), 6.8-7.9(11H, Ar-H), 6.1(1H, -N-CH-S-), 5.3(2H, -O-CH_2-CO-), 3.8(6H, -O-CH_3), 3.4(2H, -S-CH_2-), Mass (m/e value): 438.1(6%)(M^+), 439.1(5%)(M+1), 377.1(50%), 301.0(70%), 274.0(38%), 228.1(58%), 200.7(67%), 185.1(24%), 157.1(48%), 127.1(73%), 102.0(44%),100.4(100%)B.

Compound A8: N-[2-(2-chlorophenyl)-4-oxo-1,3-thiazolidin-3-yl]-2-(naphthalene-2-yloxy)acetamide. M.F- $C_{21}H_{17}ClN_2O_3S$, M.W- 412.89, M.P- 198^{0}C, R_f – 0.44, Yield-71.2%, IR (KBr) ν (cm^{-1}): 1614.07cm-1(Ar-C=C), 3188.27cm-1(Aliph-N-H), 1048.26cm-1(N-N), 1267.13cm-1(C-N), 774.55cm-1(C-S), 1685.07cm-1(C=O), 700.46cm-1(Ar-C-Cl), 1721.07cm-1(C=O-thiazolidine), ^{1}H-NMR δ (ppm): 8.4(1H, -NH-), 6.8-7.9(11H, Ar-H), 6.2(1H, -N-CH-S-), 5.2(2H, -O-CH_2-CO-), 3.7(2H, -S-CH_2-), Mass (m/e value): 412.9(14%)(M^+), 413.8(13%)(M+1), 377.1(50%), 301.0(70%), 274.0(38%), 228.1(58%), 200.7(67%), 185.1(24%), 157.1(48%), 127.1(73%), 102.0(44%),100.4(100%)B.

Compound A9: 2-(naphthalene-2-yloxy)-N-[2-(3-nitrophenyl)-4-oxo-1,3-thiazolidin-3-yl]acetamide. M.F- $C_{21}H_{17}N_3O_5S$, M.W-423.44, M.P-166^{0}c, R_f - 0.68, Yield-71.5%, IR (KBr) ν (cm^{-1}): 1612.32cm-1(Ar-C=C), 3217.42cm-1(Aliph-N-H), 1050.57cm-1(N-N), 1237.20cm-1(C-N), 703.59cm-1(C-S), 1682.57cm-1(C=O), 1507.14cm-1(Ar-NO_2), 1721.38cm-1(C=O-thiazolidine), ^{1}H-NMR δ (ppm): 8.2(1H, -NH-), 6.8-7.9(11H, Ar-H), 6.1(1H, -N-CH-S-), 5.1(2H, -O-CH_2-CO-), 3.6(2H, -S-CH_2-), Mass (m/e value): 423.5(9%)(M^+), 424.4(M+1), 377.1(50%), 301.0(70%), 274.0(38%), 228.1(58%), 200.7(67%), 185.1(24%), 157.1(48%), 127.1(73%), 102.0(44%),100.4(100%)B.

Compound A10: N-[2-(3-hydroxyphenyl)-4-oxo-1,3-thiazolidin-3-yl]-2-(naphthalene-2-yloxy)- acetamide. M.F- $C_{21}H_{18}N_2O_4S$, M.W-394.44, M.P- 187^{0}c, R_f-0.58, Yield- 62.3%, IR (KBr) ν (cm^{-1}): 1603.86cm-1(Ar-C=C), 3210.68cm-1(Aliph-N-H), 1048.26cm-1(N-N), 1258.95cm-1(C-N), 703.47cm-1(C-S), 1686.85cm-1(C=O),3610.93cm-1(O-H-Ph), 1721.63cm-1(C=O-thiazolidine), ^{1}H-NMR δ (ppm): 8.3(1H, -NH-), 6.8-7.9(11H, Ar-H), 6.1(1H, -N-CH-S-), 5.2(2H, -O-CH_2-CO-), 4.9(1H, Ar-OH), 3.3(2H, -S-CH_2-), Mass (m/e value): 394.5(26%)(M^+), 395.4(25%)(M+1), 377.1(50%), 301.0(70%), 274.0(38%), 228.1(58%), 200.7(67%), 185.1(24%), 157.1(48%), 127.1(73%), 102.0(44%),100.4(100%)B.

Evaluation of Acute Oral Toxicity [8]

In the present study acute oral toxicity of the synthesized compounds were performed by acute toxic class method. No sign of toxicity and mortality were observed at 2000 mg/kg b.w. to the group of animals, the LD_{50} value of the title compounds (A1-A10) expected to exceed 2000 mg/kg b. w. and represented as class 5 (2000 mg/kg < LD_{50} < 2500 mg/kg) From the toxicity studies the data revealed that all the synthesized compounds proved to be non toxic at tested dose levels and well tolerated by the experimental animals as there LD_{50} cut of values > 2000 mg/kg b. w.

Evaluation of anticonvulsant Activity [9-10]

Animals used: Albino wistar rats (150-200g) were used for the study. The animals were maintained in a well-ventilated room with 12:12 hour light/dark cycle in polypropylene cages.

MES induced convulsions method [11]: Seizures are induced to all the groups by using an Electro convulsiometer. Maximal electroshock seizures were elicited by a 60 Hz alternating current of 150 mA intensity for 0.2 sec. A drop of electrolyte solution (0.9% NaCl) with lignocaine was applied to the corneal electrodes prior to application to the rats. This increases the contact and reduces the incidence of fatalities. The synthesized compounds were administered for 14 days before induction of seizures. The duration of various phases of epilepsy were observed. The percentage protection was estimated by observing the number of animals showing abolition of Hind Limb Tonic Extension (HLTE) or extension not greater than 90^{o}.

RESULT AND DISCUSSION

The duration of tonic hindleg extension in rats treated with vehicle was 12.21±0.03seconds. The synthetic derivatives at dose of 200 mg/kg protect animals from seizures and significantly ($p<0.001$) reduced the duration of tonic hindleg extension for 0.5±0.69,1.2±o.69,1.9±o.98,2.5±0.36, 3.2±o.84 seconds(A9,A8,A2,A1&A10). Whereas, the standard drug phenytoin treated animals exhibits abolished tonic hindleg extension. Phenytoin treated animals have shown 100% protection against MES induced seizures where as synthetic derivatives (A9,A8,A2,A1&A10) 200 mg/kg have shown 95.85%,90.04%,84.23%,79.75% &73.44% protection respectively .

Table 1: Effect of Synthesized Thiazolidinones Derivatives on MES induced Seizures in Rats

Group	Design of treatment	Flexion	Extensor	Clonus	Stupor	Recovery	% protection
I	Vehicle control	8.9±0.32	12.21±0.03	18.78±0.32	38.2±0.58	189.2	0
II	Phenytoin 25 mg/kg, i.p.	3.9±0.33	0	8.91±0.54	16.29±0.35	93.5	100
III	A1 (200 mg/kg)	5.3±0.24	2.5±0.36	10.8±0.89	20.41±0.36	113	79.75
IV	A2 (200 mg/kg)	4.9±0.56	1.9±0.98	9.9±0.78	19.32±0.58	103	84.23
V	A3 (200 mg/kg)	6.3±0.36	4.5±0.78	12.9±0.69	25.82±0.45	134	62.65
VI	A4 (200 mg/kg)	7.8±0.25	9.8±0.45	16.7±0.25	35.9±0.32	162	18.66
VII	A5 (200 mg/kg)	7.2±0.36	7.3±0.58	15.8±0.69	35.4±0.98	153	40.29
VIII	A6 (200 mg/kg)	6.3±0.25	5.7±0.87	13.5±0.54	29.20±0.48	142	52.69
IX	A7 (200 mg/kg)	6.5±0.58	6.8±0.69	14.2±0.14	31.21±0.78	149	43.56
X	A8 (200 mg/kg)	4.4±0.69	1.2±0.35	9.5±0.12	17.92±0.65	98	90.04
XI	A9 (200 mg/kg)	4.01±0.25	0.5±0.69	9.1±0.87	16.89±0.78	95	95.85
XII	A10 (200 mg/kg)	5.7±0.35	3.2±0.84	12.2±0.58	23.4±0.45	125	73.44

Values are expressed as mean ± SEM of six observations; *$p<0.05$; ** $p<0.01$.Comparison between Group I *Vs* Group II, Group III &Group IV; Statistical significant test for comparison was done by ANOVA, followed by Dunnet's 't' test

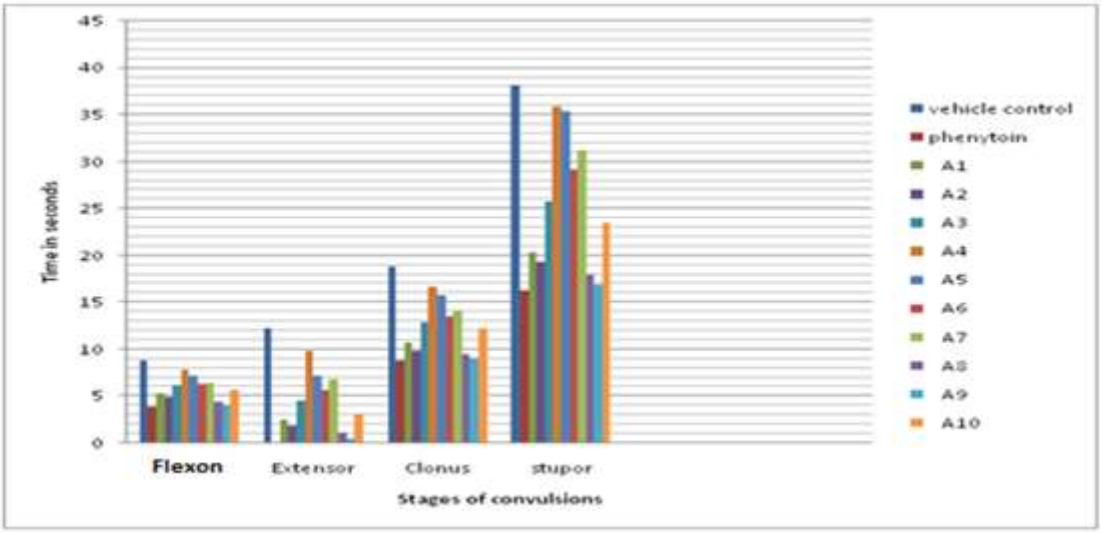


Fig.1: Stages of convulsions against time of recovery

CONCLUSION

From the present study it can be concluded that the test compounds A9, A8, A2, A1, A10 exhibit the highest anticonvulsant activity among the ten synthesized compounds. When compared with standard drug phenytoin (25 mg/kg i.p) it was found that the following synthesized compounds exhibited anticonvulsant activity in the order of A9 > A8 > A2 > A1 > A10 etc.The synthesized compounds shown the anticonvulsant activity in the order of the highest to the lowest because they contain various functional groups at different position in the aromatic ring like 3-NO_2, 2-Cl, 4- Cl, 4-OH, 3-OH etc.

REFERNCES

1. Vittoria Diurono M, Mazzoni O, Piscopo E, Calignano A, Giordano F, Bolognese A; Synthesis and antihistaminic activity of some thiazolidine-4-ones. J Med Chem., 1992; 35(15):2910-2912.
2. Barreca ML1, Balzarini J, Chimirri A, De Clercq E, De Luca L, Höltje HD *et al.*; Design and Synthesis, Structure Activity Relationships and Molecular Modeling studies of 2,3 –diaryl-1,3-thiazolidin-4-ones as Potent Anti HIV agents. J Med Chem., 2002; 45(24); 5410-5413.
3. Brown FC; 4-thiazolidinones. Chem. Rev., 1996; 61(5):463-521.
4. Jain AK, Vaidya A, Ravichandran V, Kashaw SK; Recent developments and biological activities of thiazolidinone derivatives. A review. Bioorganic and Medicinal Chemistry, 2012; 20(11): 3378-3395.
5. Zhou H, Wu S, Zhai S, Liu A, Sun Y, Li R *et al.*; Design, synthesis, cytoselective toxicity, structure activity relationships, and pharmacophore of thiazolidinone derivatives targeting drug-resistant lung cancer cells. J Med Chem., 2008; 51(5): 1242–125.
6. Vicini P, Geronikaki A, Incerti M, Zani F, Deardenc J, Hewitt M; 2-Heteroarylimino-5-benzylidene-4-thiazolidinones analogues of 2-thiazolylimino-5-benzylidene-4-thiazolidinones with antimicrobial activity: Synthesis and structure activity relationship. Bioorg Med Chem., 2008; 16(7): 3714–3724.
7. Palaska E, Sahin G, Kelicen P, Durlu NT, Altinok G; Synthesis and anti-inflammatory activity of 1-acylthiosemicarbazides, 1,3,4-oxadiazoles, 1,3,4-thiadiazoles and 1,2,4-triazole-3-thiones Il Farmaco, 2002; 57(2): 101-107.
8. "OECD guidelines – 423" for testing of chemicals. 2001:1-14.
9. Browning R; The electroshock model, neuronal network and antiepileptic drugs. In Faingold CL, and Fromm GH editors; Drugs for Control of Epilepsy: Actions on Neuronal Networks in Seizure Disorders, CRC Press. Boca Raton, FL. 1992: 195-211.
10. Otoom S, Batieha A, Hadidi H, Hasan M, Al-Saudi K; Evaluation of drug use in Jordan, using WHO Prescribing indicators. East Mediter Health J., 2002; 8(4-5): 537-543.
11. Turner RA; Screening procedures in Pharmacology. New York, Academic Press, 1972.